REMARKS

In view of the above amendments and the following remarks, the Examiner is respectfully requested to withdraw the rejections, and allow claims 1, 8, 14-16, 21, 24-26 and 32-54, the currently pending claims. New claims 47-54 are added, and claims 1, 35 and 40 are amended. Entry of Applicants' earlier filed amendments is requested. Applicants note that pending Claim 1 was omitted from the Advisory Action of September 4, 2003.

Support for the amending language "RB function is disrupted" may be found in the specification at page 22, line 9.

The Advisory Action of September 4, 2003 states that the term "selective replication in said target cell" raises issues under 35 U.S.C.112, in that the characteristics of the vector are dependent on the cell of interest. Applicants respectfully submit that the amended claims clearly define the claimed invention.

As set forth in independent claims 1 and 35, an adenovirus vector is claimed, where the vector comprises specific transcriptional regulatory elements operably linked to specific coding sequences. The language relating to selective replication provides clarification of the functional properties of the vector, which flow from the arrangement of genetic elements.

The Advisory Action further questions Applicants' teaching of essential HRE sequences. The present specification describes the transcriptional complex HIF-1, which is induced under hypoxic conditions, and which then interacts with binding sites to regulate transcription of genes, including vascular endothelial growth factor, and glycolytic enzymes, including enolase-1 (page 22, line 24 through page 23, line 4).

It was known in the art at the time of filing that the binding site for HIF-1 is a 32-base pair hypoxia-responsive element, which contains two hypoxia-inducible factor-1 (HIF-1) binding sites (HBSs). Jiang *et al.* (cited on page 49, lines 14-16), discusses increased expression in hypoxic cells is mediated in part by binding of HIF-1 to cis-acting HREs located primarily in the 5' regions of these genes (p. 5328). The paper goes on to describe (p. 5331) the use of a plasmid construct which contained a 68 bp HRE from the ENO1 gene 5' flanking region. It can be seen in Jiang *et al.* that an Eno1 HRE has the sequence starting with a 5' AGGGCCGGACGTGGGGCCCC, followed by an undefined 28 nucleotides, then the 3' sequence. Jiang et al. cite an earlier publication (Semenza et al. (1996) J. Biol. Chem 271:32529-32537) for further details about this HRE. The Semenza *et al.* paper discloses the sequence of a functional HIF-1 binding site in an HRE as "ACGCTGAGTGCGTGCGGGACTCGGAGTACGTGACGGAGCCCC". Hence, one of skill in the art

would readily be able to determine the metes and bounds of the claimed invention, as an HRE is a well-defined binding site.

Applicants note that newly added Claims 47-52 recite the inclusion in the vector of a second adenoviral gene essential for replication operably linked to a heterologous promoter. The previously cited prior art, Henderson (WO 97/01358) and Hallenbeck (WO 96/17053), do not teach or suggest an adenovirus vector for cytolysis of a target cell population; and do not teach adenovirus vectors comprising a second adenoviral gene essential for replication under the control of a heterologous promoter.

Further, the prior art is limited to transcriptional regulatory elements that provide for tissue specificity, for example prostate specific expression, liver specific replication, melanoma specific replication, *etc.* The presently claimed invention relates to transcriptional regulatory elements that could be activated in a variety of cell types dependent upon "cell status", the properties of which cell types are set forth in the claims and clearly described in the specification. It could not have been predicted from the teachings of the prior art that such "cell status" specific elements could provide specificity of replication.

The previously cited Walther *et al.*, Dachs *et al.*, Dachs *et al*, Advani *et al.* and Parr *et al.* references describe various cell status regulatory elements that are useful in gene delivery vehicles, but do not compensate for the lack of teaching in Henderson (WO 97/01358) and Hallenbeck (WO 96/17053) relative to replication-competent adenoviral vectors that exhibits selective cytotoxicity for a cell based on the state of the cell. One of skill in the art would not arrive at the claimed invention if the cited references were to be combined and the combined references do not provide a reasonable expectation of success in practicing the present invention.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number CELL-014.

Respectfully submitted,

Date: October 23, 2003

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